

**Project Title:** Development of an EV-D68 animal model

**Supervisory team:** Dr. Vinod Balasubramaniam (Monash), Prof. Wong Kum Thong (UM), Assoc Prof Ong Kien Chai (UM), Dr. Tan Soon Hao (UM)

**Project Description:**

Since 2014, human enterovirus D68 (EV-D68) has reemerged to cause severe respiratory disease worldwide, including in Asia [1]. Because person-to-person transmission of EV-D68 is mainly by the respiratory route, the potential for epidemics cannot be underestimated. In addition to severe respiratory disease, EV-D68 infection in children and young adults may give rise to debilitating central nervous system (CNS) complications such as acute flaccid myelitis (AFM) and encephalomyelitis leading to death or serious and permanent neurological sequelae [2]. So far, hundreds of children have been reported to develop CNS complications in the Western hemisphere but we predict outbreaks will occur in Malaysia and other parts of Asia, as EV-D68 is readily isolated from clinical specimens [2]. In fact, with the imminent eradication of the poliovirus worldwide, EVD68 (like enterovirus A71) is being suggested as an important cause of non-polio cause of poliomyelitis and encephalomyelitis in the near future [2-4]. Very little work has been done to produce good animal models for human EV-D68 infection and the limited existing models do not adequately mimic the human disease well [5-7]. Based on our group's previous experience developing good animal models for enteroviruses, including for Enterovirus A71 (EV-A71) [8, 9] and Coxsackievirus A16 [10], we propose to develop a small animal model by an intranasal route to study viral pathogenesis, neuroinvasion and neuropathology. Overall, the main aim is to develop therapeutics for treatment and a vaccine to be tested in vivo. This could lead to products for subsequent commercial development. A further advantage of a good animal model that can mimic human disease would be the knowledge gained from studying the neuropathogenesis of EV-D68. Moreover, the methodology involved in producing this model could potentially be patented.

**Required skills** (preferably not necessary):

1. Biomedical Sciences/Neuroscience/Molecular Virology or other equivalent Hons or Master's degree
2. Experience on experimental molecular virology (infection), animal handling techniques
3. Strong writing and analytical skills

**References**

1. Holm-Hansen, C.C., S.E. Midgley, and T.K. Fischer, Global emergence of enterovirus D68: a systematic review. *Lancet Infect Dis*, 2016. 16(5): p. e64-e75.
2. Hixon, A.M., et al., Understanding Enterovirus D68-Induced Neurologic Disease: A Basic Science Review. *Viruses*, 2019. 11(9).
3. Messacar, K., M.J. Abzug, and S.R. Dominguez, The Emergence of Enterovirus-D68. *Microbiol Spectr*, 2016. 4(3).

4. Rosenfeld, A.B., A.L. Warren, and V.R. Racaniello, Neurotropism of enterovirus D68 isolates is independent of sialic acid and is not a recently acquired phenotype. *bioRxiv*, 2017.
5. Zhang, C., et al., A Mouse Model of Enterovirus D68 Infection for Assessment of the Efficacy of Inactivated Vaccine. *Viruses*, 2018. 10(2).
6. Hixon, A.M., et al., A mouse model of paralytic myelitis caused by enterovirus D68. *PLoS Pathog*, 2017. 13(2): p. e1006199.
7. Sun, S., et al., A neonatal mouse model of Enterovirus D68 infection induces both interstitial pneumonia and acute flaccid myelitis. *Antiviral Res*, 2019. 161: p. 108-115.
8. Phyu, W.K., K.C. Ong, and K.T. Wong, A Consistent Orally-Infected Hamster Model for Enterovirus A71 Encephalomyelitis Demonstrates Squamous Lesions in the Paws, Skin and Oral Cavity Reminiscent of Hand-Foot-and-Mouth Disease. *PLoS One*, 2016. 11(1): p. e0147463.
9. Phyu, W.K., K.C. Ong, and K.T. Wong, Modelling person-to-person transmission in an Enterovirus A71 orally infected hamster model of hand-foot-and-mouth disease and encephalomyelitis. *Emerg Microbes Infect*, 2017. 6(7): p. e62.
10. Hooi, Y.T., et al., A novel orally infected hamster model for Coxsackievirus A16 hand-footand-mouth disease and encephalomyelitis. *Lab Invest*, 2020. 100(9): p. 1262-1275